PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

To:

Commissioner
US Department of Commerce
United States Patent and Trademark
Office, PCT
2011 South Clark Place Room
CP2/5C24
Arlington, VA 22202
ETATS-UNIS D'AMERIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 12 February 2001 (12.02.01)	
International application No. PCT/GB00/02118	**Applicant's or agent's file reference** SJK/BP5859236
International filing date (day/month/year) 01 June 2000 (01.06.00)	**Priority date** (day/month/year) 25 June 1999 (25.06.99)
Applicant CAWTHORNE, Michael et al	

1. The designated Office is hereby notified of its election made:

[X] in the demand filed with the International Preliminary Examining Authority on:

27 December 2000 (27.12.00)

[ ] in a notice effecting later election filed with the International Bureau on:

2. The election [X] was

[ ] was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland	Authorized officer Juan Cruz
Facsimile No.: (41-22) 740.14.35	Telephone No.: (41-22) 338.83.38

WO 01/01130
PCT/GB00/02118

PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTICE INFORMING THE APPLICANT OF THE COMMUNICATION OF THE INTERNATIONAL APPLICATION TO THE DESIGNATED OFFICES

(PCT Rule 47.1(c), first sentence)

To:
KIDDLE, Simon, J.
Mewburn Ellis
York House
23 Kingsway
London WC2B 6HP
ROYAUME-UNI

Date of mailing (day/month/year) 04 January 2001 (04.01.01)	
Applicant's or agent's file reference SJK/BP5859236	**IMPORTANT NOTICE**

International application No.	**International filing date** (day/month/year)	**Priority date** (day/month/year)
PCT/GB00/02118	01 June 2000 (01.06.00)	25 June 1999 (25.06.99)

Applicant
PROTEOME SCIENCES PLC et al

1. Notice is hereby given that the International Bureau has communicated, as provided in Article 20, the international application to the following designated Offices on the date indicated above as the date of mailing of this Notice:
   AG,AU,DZ,KP,KR,MZ,US

   In accordance with Rule 47.1(c), third sentence, those Offices will accept the present Notice as conclusive evidence that the communication of the international application has duly taken place on the date of mailing indicated above and no copy of the international application is required to be furnished by the applicant to the designated Office(s).

2. The following designated Offices have waived the requirement for such a communication at this time:
   AE,AL,AM,AP,AT,AZ,BA,BB,BG,BR,BY,CA,CH,CN,CR,CU,CZ,DE,DK,DM,EA,EE,EP,ES,FI,GB,GD,
   GE,GH,GM,HR,HU,ID,IL,IN,IS,JP,KE,KG,KZ,LC,LK,LR,LS,LT,LU,LV,MA,MD,MG,MK,MN,MW,MX,
   NO,NZ,OA,PL,PT,RO,RU,SD,SE,SG,SI,SK,SL,TJ,TM,TR,TT,TZ,UA,UG,UZ,VN,YU,ZA,ZW
   The communication will be made to those Offices only upon their request. Furthermore, those Offices do not require the applicant to furnish a copy of the international application (Rule 49.1(a-bis)).

3. Enclosed with this Notice is a copy of the international application as published by the International Bureau on
   04 January 2001 (04.01.01) under No. WO 01/01130

REMINDER REGARDING CHAPTER II (Article 31(2)(a) and Rule 54.2)

If the applicant wishes to postpone entry into the national phase until 30 months (or later in some Offices) from the priority date, a **demand for international preliminary examination** must be filed with the competent International Preliminary Examining Authority before the expiration of 19 months from the priority date.

It is the applicant's sole responsibility to monitor the 19-month time limit.

Note that only an applicant who is a national or resident of a PCT Contracting State which is bound by Chapter II has the right to file a demand for international preliminary examination.

REMINDER REGARDING ENTRY INTO THE NATIONAL PHASE (Article 22 or 39(1))

If the applicant wishes to proceed with the international application in the **national phase**, he must, within 20 months or 30 months, or later in some Offices, perform the acts referred to therein before each designated or elected Office.

For further important information on the time limits and acts to be performed for entering the national phase, see the Annex to Form PCT/IB/301 (Notification of Receipt of Record Copy) and Volume II of the PCT Applicant's Guide.

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No. (41-22) 740.14.35

Authorized officer
J. Zahra

Telephone No. (41-22) 338.83.38

Continuation of Form PCT/IB/308

NOTICE INFORMING THE APPLICANT OF THE COMMUNICATION OF THE INTERNATIONAL APPLICATION TO THE DESIGNATED OFFICES

Date of mailing (day/month/year) 04 January 2001 (04.01.01)	IMPORTANT NOTICE
Applicant's or agent's file reference SJK/BP5859236	International application No. PCT/GB00/02118

The applicant is hereby notified that, at the time of establishment of this Notice, the time limit under Rule 46.1 for making amendments under Article 19 has not yet expired and the International Bureau had received neither such amendments nor a declaration that the applicant does not wish to make amendments.

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	**FOR FURTHER ACTION**	see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.
SJK/BP5859236		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/GB 00/ 02118	01/06/2000	25/06/1999
Applicant		
PROTEOME SCIENCES PLC		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 5 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**

a. With regard to the **language**, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

[ ] the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :

[ ] contained in the international application in written form.

[ ] filed together with the international application in computer readable form.

[ ] furnished subsequently to this Authority in written form.

[ ] furnished subsequently to this Authority in computer readble form.

[ ] the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

[ ] the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. [X] **Certain claims were found unsearchable** (See Box I).

3. [ ] **Unity of invention is lacking** (see Box II).

4. With regard to the **title,**

[X] the text is approved as submitted by the applicant.

[ ] the text has been established by this Authority to read as follows:

5. With regard to the **abstract,**

[X] the text is approved as submitted by the applicant.

[ ] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No. ____

[ ] as suggested by the applicant.

[ ] because the applicant failed to suggest a figure.

[ ] because this figure better characterizes the invention.

[X] None of the figures.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 33, 39, 53-56

Present claims 33 and 39 lack support within the meaning of Article 6 PCT and disclosure within the meaning of Article 5 PCT with regard to essential technical features for the embodiments claimed, thus rendering a meaningful search over the whole of the claimed scope is impossible.

Present claims 53-56 relate to an extremely large number of possible proteins. In fact, the claims contain so many possible proteins that a lack of clarity and conciseness within the meaning of Article 6 PCT arises to such an extent as to render a meaningful search of the claims impossible. Indeed it is acknowleged that at least some of the claimed proteins e.g. POMT8 are known (Glutathione-S- Transferase) in the prior art thus indicating that the claims do not determine the subject matter for which protection is sought.

The search was limited to the use of differential protein expression in the detetection and monitoring of a condition characterised by pancreatic islet or beta cell dysfunction.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

International Application No
PC[redacted] 00/02118

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 G01N33/50 G01N33/68 C07K14/47

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 G01N C07K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, BIOSIS, WPI Data, PAJ

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
E	WO 00 46369 A (CHIRON CORP ;KENNEDY GIULIA (US)) 10 August 2000 (2000-08-10) claim 13 page 30, line 13 -page 31, line 14 page 32, line 22 -page 33, line 22 ---	1-32, 34-38, 40-52
X	WO 97 15310 A (UNI. FLORIDA RESEARCH FOUNDATION) 1 May 1997 (1997-05-01) page 18, line 21 -page 19, line 1 --- -/--	1-32, 34-38, 40-52

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
15 November 2000	24/11/2000

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Routledge, B

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Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Interna[redacted]al Application No
PC[redacted] 00/02118

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EDVARDSSON ULRIKA ET AL: "A proteome analysis of livers from obese (ob/ob) mice treated with the peroxisome proliferator WY14,643." ELECTROPHORESIS, vol. 20, no. 4-5, April 1999 (1999-04), pages 935-942, XP000964564 ISSN: 0173-0835 the whole document ---	1-32, 34-38, 40-52
X	SHIMADA A ET AL: "BETA-CELL DESTRUCTION MAY BE A LATE CONSEQUENCE OF THE AUTOIMMUNE PROCESS IN NONOBESE DIABETIC MICE" DIABETES,US,NEW YORK, NY, vol. 45, no. 8, 1 August 1996 (1996-08-01), pages 1063-1067, XP000603754 ISSN: 0012-1797 page 1064, left-hand column, paragraph F -right-hand column, paragraph 1; figure 1 -----	1-32, 34-38, 40-52

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INTERNATIONAL SEARCH REPORT

Information on patent family members

Interna[redacted]al Application No
PC[redacted] 00/02118

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 0046369 A	10-08-2000	NONE	
WO 9715310 A	01-05-1997	US 6001647 A	14-12-1999
		AU 7468396 A	15-05-1997
		CA 2235509 A	01-05-1997
		EP 0871455 A	21-10-1998
		JP 11514877 T	21-12-1999

PATENT COOPERATION TREATY

REC'D 11 JUL 2001

WIPO

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INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
SJK/BP5859236		

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/GB00/02118	01/06/2000	25/06/1999

International Patent Classification (IPC) or national classification and IPC
G01N33/50

Applicant
PROTEOME SCIENCES PLC

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 11 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☒ Certain documents cited
   - VII ☒ Certain defects in the international application
   - VIII ☒ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
27/12/2000	09.07.2001

Name and mailing address of the international preliminary examining authority:

European Patent Office
D-80298 Munich
Tel. +49 89 2399 - 0 Tx: 523656 epmu d
Fax: +49 89 2399 - 4465

Authorized officer

Knudsen, H

Telephone No. +49 89 2399 8696

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/GB00/02118

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:
Description, pages:

1-91 as originally filed

Claims, No.:

1-56 as originally filed

Drawings, sheets:

1/14-14/14 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:

☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application.

☒ claims Nos. 33-34,36-37,39,41-42,44-45,50-56 (N,IS,IA) .

because:

☒ the said international application, or the said claims Nos. 44-45,50 (IA) relate to the following subject matter which does not require an international preliminary examination (*specify*):
see separate sheet

☒ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. 34,36-37,41-42,44-45,50-52 are so unclear that no meaningful opinion could be formed (*specify*):
see separate sheet

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☒ no international search report has been established for the said claims Nos. 33,39,53-56.

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

☐ the written form has not been furnished or does not comply with the standard.

☐ the computer readable form has not been furnished or does not comply with the standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N) Yes: Claims 1-32,35,38,40,43

	No:	Claims	46-49
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-32,35,38,40,43
Industrial applicability (IA)	Yes:	Claims	1-32,35,38,40,43,46-49
	No:	Claims	

2. Citations and explanations
see separate sheet

VI. Certain documents cited

1. Certain published documents (Rule 70.10)

and / or

2. Non-written disclosures (Rule 70.9)

see separate sheet

VII. Certain defects in the international application

The following defects in the form or contents of the international application have been noted:
see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:
see separate sheet

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

3.1 Claims 44, 45 and 50 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

3.2 As explained in the International Search Report (ISR), claims 33, 39 and 53-56 could not be searched due to lack of clarity and support in the description.

3.3 The IPEA is of the opinion that claims 34 and 36-37, all of which refer to claim 33, are not examinable for lack of clarity and support in the description for the reasons given for claim 33 in the ISR. Claims 41-42, 44-45 and 50 define the agent mentioned in these claims the same way as does claim 39, ie by its identifiableness by the method of claims 1-38. These claims therefore cannot be examined for the same reasons as claim 39, In claims 51-52, the agent used for the treatment is not defined at all by technical features and these claims are therefore also unexaminable.

Re Item V

Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

The closest prior art document cited in the International Search Report is :

D1: Edvardsson U et al: 'A proteome analysis of livers from obese (ob/ob) mice treated with the peroxisome proliferator WY14,643.' ELECTROPHORESIS, vol. 20, no. 4-5, April 1999, pages 935-942, ISSN: 0173-0835

NOVELTY & INVENTIVE STEP:

5.1 The method of claim 1 is directed to an assay for screening for agents which are useful in the treatment of islet or β-cell dysfunction. The steps of the method are:

1) Obtaining a sample from a subject who/which has been treated with the agent;
2) determining the degree of expression of a protein, which is differentially expressed in subjects with different levels of islet or β-cell function;
3) selecting/rejecting the agent on the basis of the change of expression caused by the agent.

D1 discloses a method in which ob/ob mice which have reduced β-cell function are treated with WY14,643, a peroxisome proliferator activated receptor (PPAR) agonist. The specific proteins expressed in liver samples taken from treated and untreated mice is compared after 2D- gelelectrophoresis. A number of enzymes, which form part of the peroximal β- oxidation chain, and are expressed in higher amounts in the treated mice are identified. The effectiveness of WY14,643 is determined on the basis of the upregulation of this peroximal β-oxidation pathway. However, the method differs from the method of D1 in that it does not have the purpose of finding agents useful in treating conditions characterised by islet or β-cell dysfunction.

The applicants argue that the method of claim 1 also differs in that the tissue is taken from pancreatic islets or β-cells. The IPEA is not convinced by this argument because claim 1 encompasses the use of any relevant tissue. Given that liver contains tissue which is known to reflect many metabolic changes there is no doubt that liver tissue is also relevant for studying the effect of the treatment of an agent with an effect on diseases characterised by islet or β-cell dysfunction. Thus, the only difference between claim 1 and D1 lies in the purpose of finding agents having an effect on the said diseases.

The applicant further argues that the present application which shows differentially expressed proteins in connection with the treatment with one single compound open the doors for the skilled person to realise that any agent can be identified by observation of protein influenced by the treatment.

In agreement with this view, the IPEA is of the opinion that D1 shows to the skilled person that a method for identifying agents with an effect on diseases characterised by islet or β-cell dysfunction can be designed on the basis of the method of D1 and that the method of claim 1 is therefore not inventive.

Probably the skilled person would use tissue even more likely to show changes in response to the agent than liver tissue, eg islets or β-cells. Even if claim 1 was limited to the use of islet or ß-cell tissue, it would therefore not be inventive.

5.2 The selections mentioned in claims 2-5, 7, 12, 20-21 and 32 are not further removed from D1 than claim 1 and therefore lack an inventive step for the same reasons as claim 1.

5.3 The features of claims 6, 8-11, 13-19 and 22-31 are routinely employed in experimental work using the NIDDM model mice and therefore do not seem to add anything inventive to claim 1.

Another reason for the subject-matter of these claims not being considered inventive is that D1 shows that it is known in the art to establish differential protein profiles between treated and untreated mice with a reduced β-cell activity and to use lean mice with a normal β-cell activity as control. As explained in D1, Ref.20 in D1 concerns the finding of differential protein profiles between treated and untreated lean normal mice and therefore shows that the skilled person would consider carrying out such comparisons as well. Finally, it is well-known in the context of clinical trials to use healthy persons as controls to observe the effects of the medicament studied.

5.4 An additional reason for the subject-matter of claims 1-32 lacking an inventive step is that the application does not show that a technical problem is solved by the claimed method. The application does not demonstrate that the proteins identified (or the proteins identifiable) by the protocol mentioned therein are in fact markers for an improved β-cell function. The description only mentions treatment with a single drug and though the drug is known to have a certain effect against NIDDM, it cannot be deduced whether the changed protein profile is related to the positive effect on the β-cells.

The applicant argues on the basis of the results obtained with rosiglitazone and ob/ob mice that the found protein profile shown in the description is an indicator of effect on the pancreatic islet and β-cell dysfunction. However, the claimed method is much broader and even if the rosiglitazone induced profile was shown to be characteristic, the application contains no evidence which shows that a technical problem is solved in the entire breadth of the claims.

5.5 For the same reasons, the application does not contain evidence that it is possible to identify an agent with an effect on β-cell dysfunction by the method of claim 35.

5.6 The screening by HTS is well-known in the field. Claim 38 therefore does not add anything inventive to claim 1.

5.7 The same objection as raised in Paragraph 5.4 above apply, mutatis mutandis, to the medical use of the proteins identified by internal designations in claims 40 and 43. The fact that these proteins are differentially expressed in mice treated with a NIDDM drug, rosiglitazone, does not demonstrate that the proteins, per se, have any effect against any disease. Claims 40 and 43 therefore do not appear to solve a technical problem and are not considered inventive.

5.8 Claims 46-49 are based on the measurement of a protein, which is known to be differentially expressed in subjects having different β-cell activity, in a sample and assessing the subject's β-cell activity to this measurement. Claims 46-49 therefore merely repeat the basis for all diagnostic methods and are therefore not novel.

INDUSTRIAL APPLICABILITY:

5.9 For the assessment of the present claims 44, 45 and 50 on the question whether they are industrially applicable, no unified criteria exist in the PCT. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

5.10 Insofar as the subjects mentioned in claims 1-32, 35, 38, 46-49, are humans some Regional authorities will not consider these claims industrially applicable.

Re Item VI

Certain documents cited

Certain published documents (Rule 70.10)

Application No Patent No	Publication date *(day/month/year)*	Filing date *(day/month/year)*	Priority date *(not checked)* *(day/month/year)*
WO 00/46369	20.10.2000	02.02.2000	02.02.1999

The above document is published after the present application's filing date, but may become relevant prior art for those parts of the present application, if any, which do not have a valid claim to priority, in the Regional phase of the present application.

Re Item VII

Certain defects in the international application

7.1 Contrary to the requirements of Rule 5(a)(ii) PCT, the closest prior art document D1 are not identified in the description and the relevant background art disclosed therein is not briefly discussed.

7.2 It is not possible to incorporate the teaching of a prior art document into the present application's disclosure by the expression "herein incorporated by reference" or equivalents thereof (see p.91) (cf PCT Guidelines, C-II, 4.17).

7.3 Contrary to the PCT Guidelines C-II 4.16-4.17, registered trade marks used in the description have not been identified as such.

Re Item VIII

Certain observations on the international application

8.1 The present claims lack support in the description for a plurality of reasons: Firstly, the only experimental work carried out consists in the treatment of obese mice with rosiglitazone; isolation of samples of pancreatic cells from treated and untreated obese mice and from lean mice; and identification of proteins which are differentially expressed in the different samples. This work is not sufficient to demonstrate that these proteins function as markers for β-cell function or have any therapeutic effect, as explained in Item V. The skilled person who wishes to practise the invention (ie who wishes to establish whether and which proteins function as reliable markers for β-cell function or whether they have therapeutic activity) would be confronted with an undue burden. The applicant argues that the present invention opens the possibility for the skilled person to carry out the invention with any agent and protein profile. However, the IPEA does not find this argumentation convincing in respect of the undue burden which is occasioned by the endless number of possible variations encompassed by the claims.

8.2 Moreover, claim 1 lacks clarity because it is not clear which steps are intended by the expression "establishing a paradigm ...". The applicant explains that paradigm should be understood to encompass the comparisons shown on pages 26-27 of the description. Since the claims should be comprehensible when read alone (PCT-Guidelines C-III 4.2) this argumentation does not cause the IPEA to waive its objection.

8.3 It is not clear how the expression must be differentiated in order that a protein is considered differentially expressed when more than two groups of samples are compared. Claims 8-11 therefore lack clarity.

8.4 Claims 7 and 20 appear to be identical. One of these claims therefore should be deleted for reasons of conciseness.

8.5 The methods of claims 12-19 lack clarity because it is not clear which groups of subjects are compared when establishing the paradigm.

8.6 The use of internal designations (POM6 ...) in the claims is not allowable as the claims should be comprehensible on their own (Guidelines C-III 4.2). The designations should therefore be replaced by scientifically accepted names when possible and by definitions based on physical characteristics when this is not possible.